Introduction to the Conference on Beryllium-related Diseases

C. W. Jameson

National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina

— Environ Health Perspect 104(Suppl 5):935–936 (1996)

This issue of *Environmental Health Perspectives Supplements* includes papers presented at the Conference on Beryllium-related Diseases held November 8–10, 1994, at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. Beryllium is the lightest of all solid and chemically stable substances and is used in some form in the aerospace, nuclear, telecommunications, and computer industries, as well as in ceramics, dental alloys, scientific equipment, automotive parts, and tool and die making. In the United States, it is estimated that there are approximately 8000 plants with 30,000 workers who may be potentially exposed to beryllium.

The potential hazards of exposure to compounds of beryllium were first recognized in the 1930s and 1940s with reports of pulmonary disease following exposure to beryllium compounds (*1–3*). It was also in the 1940s that fluorescent light manufacturers used beryllium in their lamp phosphors, which caused widespread poisoning among workers and consumers until the industry discontinued its use in 1949. The first cases of delayed chemical pneumonitis caused by beryllium were reported in 1946 (*4*). The cases reported were found among former employees of fluorescent-lamp plants and established the clinical and morphological characteristics of berylliosis. It was not until recent developments in molecular genetics (*5*) and immunopathology (*6*) that major advances in the understanding of beryllium-related disease have taken place.

This paper was presented at the Conference on Beryllium-related Diseases held 8–10 November 1994 in the Research Triangle Park, North Carolina. Manuscript received 29 April 1996; manuscript accepted 2 May 1996.

Address correspondence to Dr. C.W. Jameson, National Institute of Environmental Health Sciences, PO Box 12233, Research Triangle Park, NC 27709. Telephone: 919-541-4096. Fax: 919-541-2242. E-mail: jameson@niehs.nih.gov

The meeting highlighted several major areas of concern regarding beryllium-related diseases. Subjects discussed at this conference included chronic beryllium disease and beryllium sensitization, the lymphocyte proliferation test, industrial experience with workers exposed to beryllium, industrial hygiene assessment of beryllium-exposed workers, mechanisms in chronic beryllium disease pathogenesis, animal studies related to chronic beryllium disease and cancer, carcinogenicity studies of workers exposed to beryllium, occupational medical programs for current and past exposed workers, future research needs related to chronic beryllium disease, and medical and ethical issues related to chronic beryllium disease.

It is clear from the presentations and discussions at this conference that there are still many questions to be answered regarding beryllium-related diseases. The discussions concerning research needs were broad and included the following five areas:

Toxicology. There is a need to continue to develop animal models for chronic beryllium disease. Gregory Finch of the Inhalation Toxicology Research Institute/ Lovelace Research Institute gave an overview talk titled "Animal Models of Beryllium-induced Lung Disease," which is included in the papers from this conference. Keith Meyer of the Department of Medicine, Section of Pulmonary and Critical Care Medicine of the University of Wisconsin Medical School reported on his investigations of the role of variations in major histocompatibility (MHC) gene expression in susceptibility to the granulomagenic effects of beryllium. Dr. Meyer discussed his attempt to induce granulomatous lung inflammation in mouse strains that varied in MHC class II antigen haplotypes. He was able to induce granulomatous lung inflammation in strain A (H-2^a MHC haplotype) mice via intratrachel installation of beryllium sulfate. His attempts to induce such inflammations in BALB/c (H-2^dMHC haplotype) nC57BL/6 (H-2^b haplotype) mice were unsuccessful. Dr. Meyer indicated that the use of this model with manipulation of the MHC complex or other genes important in immune-medicated lung disease or the use of transgenic mice with specific gene deletions may give important insights into mechanisms by which beryllium induces a granulomatous inflammatory response in the lung (*7*).

The overall consensus from the conference concerning this topic was that research into the development of animal models should include linking immunopathology with the development of a mouse model. Toxicology studies also need to be designed to address the effect of chronic versus acute exposures.

Biomarkers. The beryllium lymphocyte proliferation test (BeLPT) must continue to be developed. Emmanuel Ojo-Amaize of Specialty Laboratories Inc. presented information on an *in vitro* immunization system used to generate beryllium-specific lymphocytes from healthy individuals who have not been exposed to beryllium. Proliferative responses of *in vitro* sensitized lymphocytes were measured by [^{3}H]thymidine uptake after secondary stimulation with beryllium salts. Analysis of lymphocytes from 52 individuals demonstrated that there is considerable variation among individuals in their capacities to be sensitized to beryllium salts *in vitro,* i.e., individuals can be classified as responders or nonresponders depending on their levels of reactivity. It is unknown whether the level of response *in vitro* correlates with the capacity to be sensitized to beryllium dust *in vivo* (*8*).

The development of the BeLPT should include cooperation between laboratories to better characterize and minimize sources of interlaboratory variability. There is also a need to obtain enough data to make a determination of when the BeLPT can move from an experimental test to a clinical tool. This will require that a scheme be developed for proficiency testing, the establishment of stable cell clones, and adequate quality control. There also needs to be continued basic cellular and molecular biology research to identify additional biomarkers for beryllium-related diseases.

Primary Prevention. There is a need to develop adequate exposure assessment data, which will be critical for the interpretation of current epidemiology studies.

There is also the need for investigators to better understand the chemical properties of the beryllium oxides versus other alloys and the physical properties of their respirable aerosols versus total particulates.

Exposure control is also an important area for further research. Investigations into the effect of excursions versus work performance and conduct are needed. Worker-based methods to further reduce exposure, including personal sampling and real-time monitoring investigations, also need to be conducted.

Secondary Prevention. Medical monitoring must continue and use data from current screening efforts to develop consensus guidelines for chest X-rays, BeLPTs, etc. These guidelines should also address whom to screen, how the screen should be conducted, when the screens should be done, etc.

Surveillance programs are also critical to allow for the systematic collection of data. A registry of beryllium-sensitized individuals could be established that could be a life-long monitoring program to insure continuous medical follow-up and serve as a resource for studies of the natural history of beryllium-related diseases.

Tertiary Prevention. Additional clinical and longitudinal epidemiology studies to investigate the natural history of beryllium-related diseases are needed. The clinical studies should ask questions to address the basic biology of the diseases as well as their natural history.

It was felt that the priorities for the research should first address the natural history of beryllium-related diseases, closely followed by medical screening and surveillance guidelines, and exposure assessment and control.

This conference, as is evident in the papers that follow, was able to bring together investigators conducting research on beryllium-related diseases and provide a forum for the discussion of some of the exciting recent advances in understanding chronic beryllium disease. I thank all those individuals who participated in the conference. I especially thank Rick Hornung, Peter Infante, and Paul Wambach, whose planning, suggestions, and organization were instrumental in making the conference a success. A special thanks goes to Merril Eisenbud, who originally proposed the idea for this conference and was very helpful in the development of the final program. I am also deeply indebted to the Joyce Daye for her hard work in administratively coordination of all the speakers and clerical assistance in the preparation of these proceedings.

REFERENCES

1. Weber H, Englehardt WE. Anwendung bei der Untersuchungen von Stauben aus der Berylliumgewinnung. Zentralbl Gewerbehyg Unfallverhuet 10:41 (1933).
2. Fabroni SM. Pulmonary pathology of beryllium powders. Med Lavoro 26:297 (1935).
3. Hyslop F, Palmes ED, Alford WC, Monaco AR, Fairhall LT. The Toxicology of Beryllium. Bulletin 181. Washington:U.S. Public Health Service, 1943.
4. Hardy HL, Tabershaw IR. Delayed chemical pneumonitis occurring in workers exposed to beryllium compounds. J Ind Hyg Toxicol 28:197 (1946).
5. Richeldi L, Sorrentino R, Saltini C. HLA-DPB1 glutamate 69: a genetic marker of beryllium disease. Science 262:242–244 (1993).
6. Newman LS, Kreiss K, King TE, Seay S, Campbell PA. Pathologic and immunologic alterations in early stages of beryllium disease: re-examination of disease definition and natural history. Am Rev Respir Dis 139:1479–1486 (1989).
7. Huang H, Meyer KC, Kubai L, Auerbach R. An immune model of beryllium-induced pulmonary granulomata in mice. Lab Invest 67(1):138–146 (1992).
8. Ojo-Amaize EA, Agopian MS, Peter JB. Novel *in vitro* method for identification of individuals at risk for beryllium hypersensitivity. Clin Diag Lab Immunol 1:164–171 (1994).